Lasers in Surgery and Medicine 26:186–195 (2000)

Nonablative Skin Remodeling: Selective Dermal Heating with a Mid-infrared Laser and Contact Cooling Combination

E.V. Ross, MD,[1]* F.P. Sajben, MD,[1] James Hsia, PhD,[2] David Barnette, MD,[1] Charles H. Miller, MD,[1] and Joseph R. McKinlay, MD[1]

[1]Department of Dermatology, Naval Medical Center San Diego, San Diego, California 92134
[2]Candela Corporation, Wayland, Massachusetts 01778

Background and Objective: **Many of the microscopic changes associated with photodamage reside in the dermis. It follows that subsurface heating of the skin might allow for cosmetic enhancement without loss of the epidermis. Accordingly, we investigated the clinical and microscopic changes produced by a mid-infrared laser coupled with a contact cooling device.**
Study Design/Materials and Methods: **Nine patients were treated with an erbium glass laser and sapphire cooling handpiece in contact with the skin. Postauricular sites were irradiated with pulse energies varying from 400–1,200 mJ and numbers of pulses from 4 to 40. Outcome measures included pain, edema, and erythema at predetermined postoperative intervals. Biopsies were performed just after treatment and 2 months postoperatively for selected pulse energy-pulse number combinations.**
Results: **Erythema, edema, and pain increased with pulse energy and number of pulses. Likewise, immediate epidermal necrosis and subsequent scarring were observed for larger pulse energy-pulse number combinations. At sites with epidermal preservation, on biopsy, immediate dermal thermal damage was observed in a band-like pattern. The deep boundaries of this band were dependent on pulse energy and pulse number. After 8 weeks, biopsies showed dermal fibroplasia roughly correlating to the band of immediate dermal thermal damage.**
Conclusion: **Selective dermal heating can be achieved with a mid-infrared laser coupled to a contact surface cooling device. In this study, the range of fibroplasia and lack of clinically substantial cosmetic enhancement suggest that the dermal thermal damage achieved may be too deep and that the injury should be confined to more superficial levels to alter the most severely photodamaged dermis. Lasers Surg. Med. 26:186–195, 2000.** **Published 2000 Wiley-Liss, Inc.**†

Key words: non-ablative; laser; cooling; remodeling

INTRODUCTION

Traditional resurfacing techniques sacrifice the epidermis. The subsequent loss of barrier function results in discomfort and desiccation-induced extension of the original wounding depth [1]. Transudation, focal crusting, and edema are generally observed during the period of dermal exposure [2–4]. Epidermal loss also increases the risks of hyperpigmentation, hypopigmentation, and infection. Because the microscopic changes associated with wrinkles occur principally in the dermis, epidermal removal may be unnecessary for improvement of facial rhytides [5,6]. Moreover, recent studies of CO_2 laser resurfacing support collagen denaturation and new collagen de-

*Correspondence to: E.V. Ross, MD, Department of Dermatology, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134.
E-mail: evross@nmcsd.med.navy.mil

Accepted 15 June 1999

position as the primary mechanisms for wrinkle reduction [7–9].

Nonablative dermal remodeling (or selective dermal heating) can be accomplished by combining a surface-cooling device with a deeply penetrating laser beam. In animal studies (EV Ross, unpublished observations), a combination of contact surface cooling and erbium glass laser (1.54 μm) irradiation resulted in dermal injury with epidermal preservation. In this farm pig model, reproducible bands of collagen denaturation were demonstrated in the superficial and deep reticular dermis. Significant gross immediate wound shrinkage (> 2% by area), was observed only where there was complete collagen denaturation microscopically, as indicated by basophilic changes on hematoxylin and eosin-stained sections. These changes typically occurred in a band extending from 400–1,200 μm below the skin surface. Basophilic staining collagen in some cases persisted for 14 days superficially (from 400–800 μm deep to the surface), and as long as 1 month in the deeper dermis (800–1,200 μm from the skin surface). Although there was epidermal preservation in these sites with severe collagen denaturation, during subsequent wound healing, pitted scarring was observed. In samples with less aggressive heating, immediate shrinkage was not observed; however, gross or microscopic changes in the heated versus untreated ends of the same specimen were usually indistinguishable.

On the basis of findings in the pig, we undertook a human study by using the same device to examine whether selective dermal heating was practical, safe, and effective. Most importantly, we wanted to examine the treatment response in solar-damaged skin in a human model.

MATERIALS AND METHODS

Laser

A flash lamp-excited erbium glass laser (λ = 1.54 μm, Candela Corp., Wayland, MA) produced pulse energies up to 1.2 J with a pulsewidth of 1 msec (nominal). Pulse energies were verified by a calibrated energy meter (Coherent, Palo Alto, CA). The laser was fired in a multiple pulsed mode with a frequency of 8 Hz.

The system was configured with a handpiece chilling system. The laser head was attached to a proprietary chilling hand piece (Fig. 1) by a 1-mm quartz fiberoptic cable. Chilled infrared-transmissive electronic liquid (Flourinert, 3M, St. Paul, MN) circulated through insulated plastic tubing at a temperature of −10°C. The tubing was connected to inlet and outlet ports on the handpiece, whose specially designed optics produced a 5-mm spot at the skin surface. The beam was nearly collimated at the skin surface, i.e., there was no attempt to spare the epidermis by targeting a certain depth at a focal point deep to the surface (vide infra). The chilled coolant flowed between the lens and a 0.5-mm-thick skin contacting sapphire window.

Fig. 1. Photograph of the handpiece apparatus. The chiller tubing is covered by overlying foam insulation.

Patient Selection

Nine patients were included in the study. There were 8 men and 1 woman. The mean age was 74 years. Patients were excluded for pregnancy, predisposition for hypertrophic scar or keloid, history of recent facial resurfacing or collagen injection in the past 2 years, use of Accutane or oral retinoids in the past 2 years, presence of collagen vascular disease, or if immunocompromised.

Methods

Seven postauricular sites were irradiated on each patient, four on one side and three on the other. Six of the sites were followed clinically for the 2-month-long study period. The other site served as a biopsy donor for the immediate postoperative period. Four India ink tattoos were placed to demarcate each of the seven treatment sites. In each patient, one side was treated with one pass of the laser. The other side was treated with two passes, usually with identical heating and cooling parameters; the excep-

TABLE 1. Numbers of Sites (Underlined) for Each Set of Laser Settings

Pulses/ pass	Passes	Total pulses	400 mJ	600 mJ	800 mJ	1000 mJ	1200 mJ
4	1	4					1[a]
4	2	8					1[a]
6	1	6			1	1[a]	
6	2	12			1	1[a]	
8	1	8	3	3	7	2[a]	
8	2	16	3	4	6		
12	1	12	2	4	2[a]		
12	2	24	2	2[a]			
24	1	24	2	1[a]			
24	2	48	2	1[a]			
32	1	32	1				
40	1	40	1				

[a]Indicates settings associated with immediate whitening and scarring.

tion was when one pass caused obvious epidermal necrosis, wherein we substituted an additional one pass treatment with lesser pulse energies or number of pulses. Finally, to rule out tissue alterations from contact cooling alone, we treated an eighth site in each patient with no laser energy.

The cooled sapphire window remained in contact with the skin during the entire series of laser pulses; that is, the skin was continuously cooled during laser irradiation. At each treatment site, the handpiece was applied to the skin for 2 seconds at −10°C, followed by a series of laser pulses delivered at 8 Hz. Pulse energies ranged from 400 to 1,200 mJ. The 2-second precooling period was designed into the control software, that is, the laser would not fire until 2 seconds after the foot pedal was activated. Where two passes were made, the second overlapping pass followed the first pass within 3–5 seconds. The handpiece was removed briefly from the skin and returned to the surface, after which the second series of pulses began after the built in 2-second delay (precooling). The second pass was designed to assess the epidermal tolerance for overlapping passes. Unlike traditional resurfacing, in nonablative remodeling, the clinician may not have immediate visual feedback as to where he has irradiated; it follows that the laser parameters should allow for direct overlapping with continued epidermal preservation. A summary matrix of all of the pulse energy-pulse number combinations is included in Table 1. The order of pulse energies (cephalad to caudal) was randomized to control for anatomic variations over the region. Clinical parameters of pain, erythema, edema, and pigment alteration were graded on a 0–4 scale by investigators blinded to the specific laser parameters. The parameters were measured immediately postoperatively, then weekly for 1 month, and finally at 2 months. Scar formation was recorded as being present or absent at 1 and 2 months. A punch biopsy (2 mm) was taken from one treatment site in each patient immediately postoperatively and at 2 months. These specimens were obtained from treated postauricular sites at various pulse energy-pulse number combinations in selected patients. For anesthesia, 1% lidocaine with 1:100,000 epinephrine was injected at the site just before biopsy. The specimens were fixed in 10% formalin. Tissue samples were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Investigators (FPS, EVR, and DJB) reviewed the specimens and characterized the initial thermal injury and subsequent fibroplasia with an ocular micrometer.

RESULTS

Clinical Data

Immediate postoperative changes included erythema, edema, and in some instances, epidermal whitening. These changes correlated positively with pulse energy and number of pulses. Immediate changes could be divided broadly into three groups. First, where there was immediate whitening, a “balling up” of the skin was observed. At the end of irradiation, the sites appeared as white firm hemispheres approximately 4 mm in diameter with a peripheral ~2 mm rim of erythema. A second group showed only slight edema and erythema, whereas a third group showed no gross changes. Pain was dependent primarily on pulse energy (Fig. 2), and there was a tendency for pain to crescendo during any pulse series. No patient required local anesthesia except for the biopsy sites. Scar formation was usually associated with immediate epidermal whitening, and tended to occur with increasing *pulse energy* and *pulse number*, as outlined in Figure 3. For pulse energy-pulse number combinations that did not result in immediate epidermal whitening, there was erythema and edema (Figs. 4a,b, 5) that persisted for not longer than 2 weeks, after which these sites were grossly indistinguishable from untreated skin. For sites exceeding this threshold, initial epidermal whitening resulted in erosions and sometimes ulcers (Fig 6a,b). These ar-

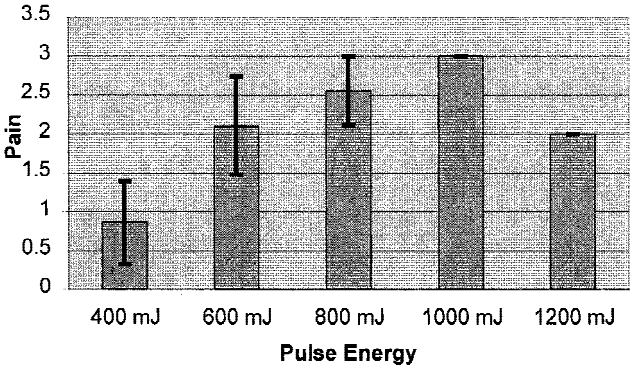

Fig. 2. Pain versus pulse energy. The smaller value for 1,200 mJ was probably attributable to the small number of sites and pulses. (Only one patient was treated at this pulse energy-pulse number combination). Error bars = ± 1 SD.

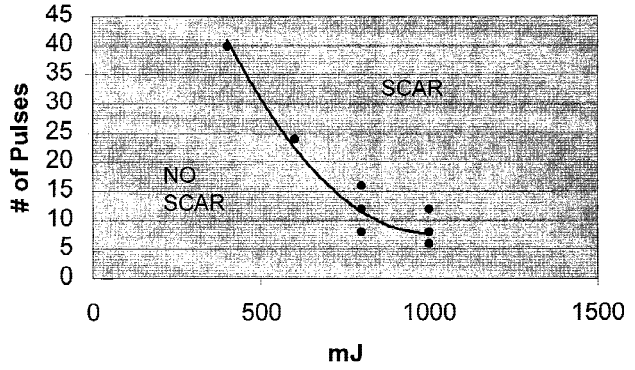

Fig. 3. The curved line in the graph shows where scarring was observed. Points to the right and superior of this line were associated with scarring, whereas those points to the left and inferior to the line typically did not show clinical scarring.

eas developed atrophic scarring at 1–2 months (Fig 7). Overall, the tissue effects were similar for one or two passes, that is, overlapping passes with a 3- to 5-second interval did not increase epidermal whitening and scarring. Cooling alone caused only mild erythema that resolved within 10 minutes after application.

Although the curve in Figure 3 usually "separated" those laser settings associated with scarring from those associated with uneventful healing, there were exceptions, as follows: One patient treated in excess of the scar "threshold" developed no pitting. This patient was treated with 16 pulses per pass at 800 mJ per pulse; most patients could not tolerate more than 8 pulses at this pulse energy. Also, two patients developed mild focal central atrophy in areas without immediate epidermal whitening. These "pits" occurred with settings below the "scar" threshold. Clinical resolution of any incidental wrinkling within the

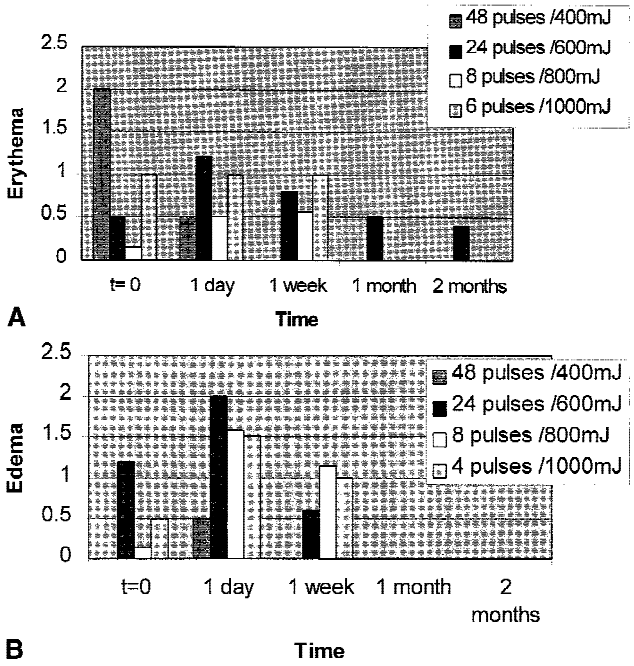

Fig. 4. **A:** Erythema for representative laser parameters for two passes (see matrix of settings in Table 1). **B:** Edema for representative laser settings for two passes.

treatment areas was not seen. Pigment alteration was not observed in any patient.

Histologic Data

At sites without gross epidermal necrosis, epidermal preservation and slight tinctorial changes in collagen staining were observed in a band from 400 to 1,300 μm deep to the skin surface. The deep boundaries of this band increased with pulse energy and pulse number. The microscopic changes were more apparent in the two-pass specimens, regardless of laser parameters. The damaged dermis demonstrated unusual clumping of basophilic collagen and elastotic material that coincided with heat-induced changes of the follicular epithelium and sebaceous glands at the same depth (Fig 8). The mean depth of injury was 703 μm, and the thickness of the band of thermally altered collagen averaged 518 μm.

At 2 months, some biopsies showed zones of dermal fibroplasia without epidermal changes (Fig 9). The increased number of fibroblasts were observed at depths roughly corresponding to the zones of heat-induced changes seen initially. Fibroplasia was not observed less than 400 μm from the skin surface. The thickness of the fibroplasia band averaged 760 μm, and the center of the band averaged 980 μm from the skin surface.

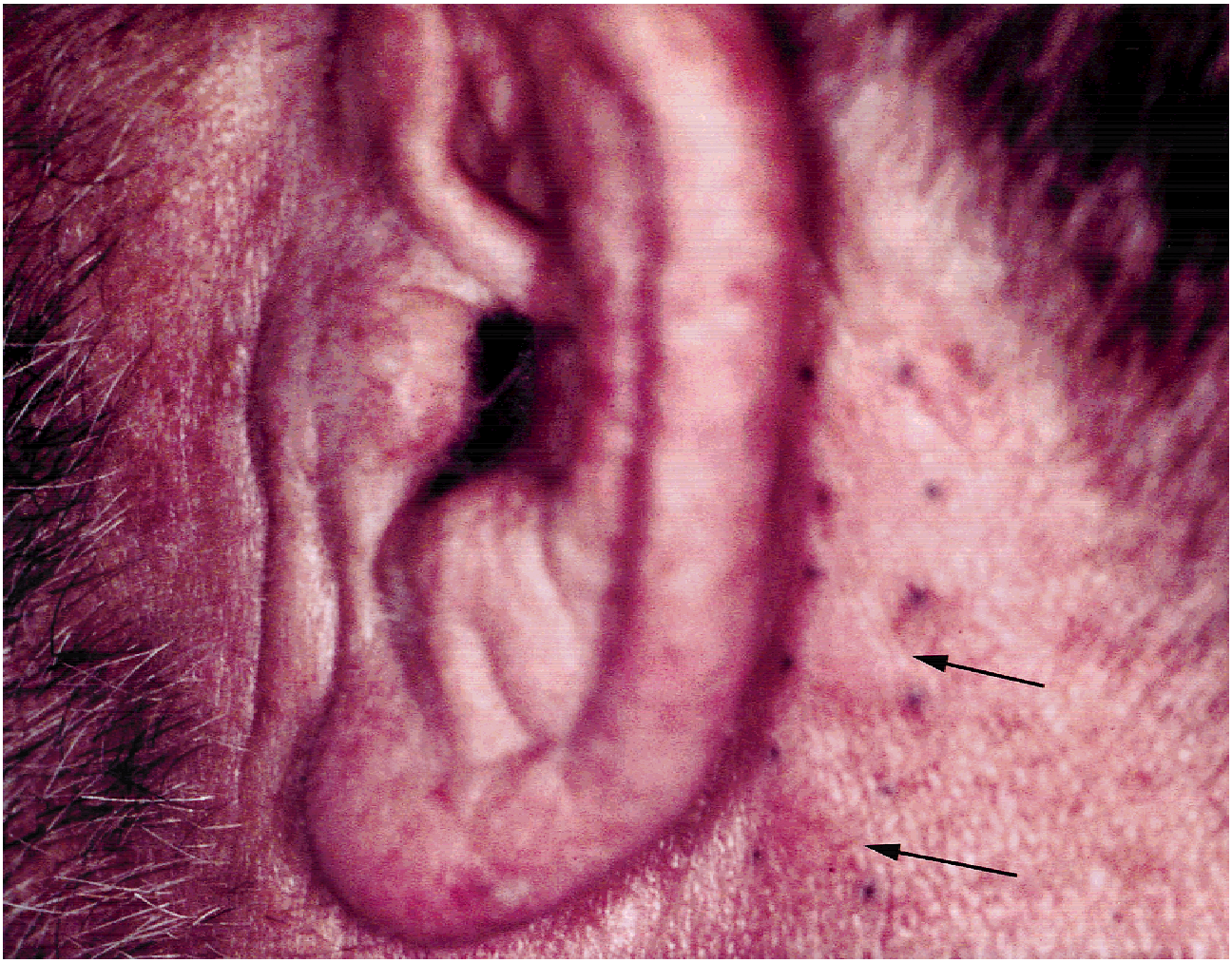

Fig. 5. Clinical photograph from patient treated with 1 pass 600 mJ/12 pulses (top arrow), and 1 pass 800 mJ/8 pulses (bottom arrow). Note slight erythema and edema, almost like a mosquito bite reaction.

Monte Carlo Model

A Monte Carlo tissue optics and heat-diffusion model was applied before the experiment to assist in the selection of optimal cooling and laser-heating parameters. A representative plot is shown in Figure 10. The model predictions for the zone of peak tissue heating were consistent with the depth and ranges of thermal damage seen in the experiment.

DISCUSSION

After traditional CO_2 resurfacing, a thin layer of papillary and sometimes superficial reticular dermis is thermally altered. Temperatures greater than 60–65°C have been shown to shrink collagen along its long axis for exposures of 90 seconds or greater [10–13]. For millisecond time exposures in laser skin remodeling, the threshold temperatures for denaturation are probably higher, likely to be in the range of 90–120°C [14,15]. After CO_2 laser skin resurfacing (LSR), we have shown that denatured collagen persists up to 10 days after injury, and the damaged extracellular matrix (ECM) appears to be integrated into newly formed granulation tissue [16]. It is believed that this shrunken collagen behaves as scaffolding for the deposition of nascent collagen, which allows for dermal remodeling and subsequent cosmetic improvement. Even where there is no dermal ablation, but only heating of a fine layer of papillary dermis, one observes zones of fibroplasia associated with new collagen deposition. Moreover, with chemical peels, cosmetic enhancement is observed despite the absence of dermal ablation. It follows that by merely heating the dermis, one could expect collagen shrinkage and

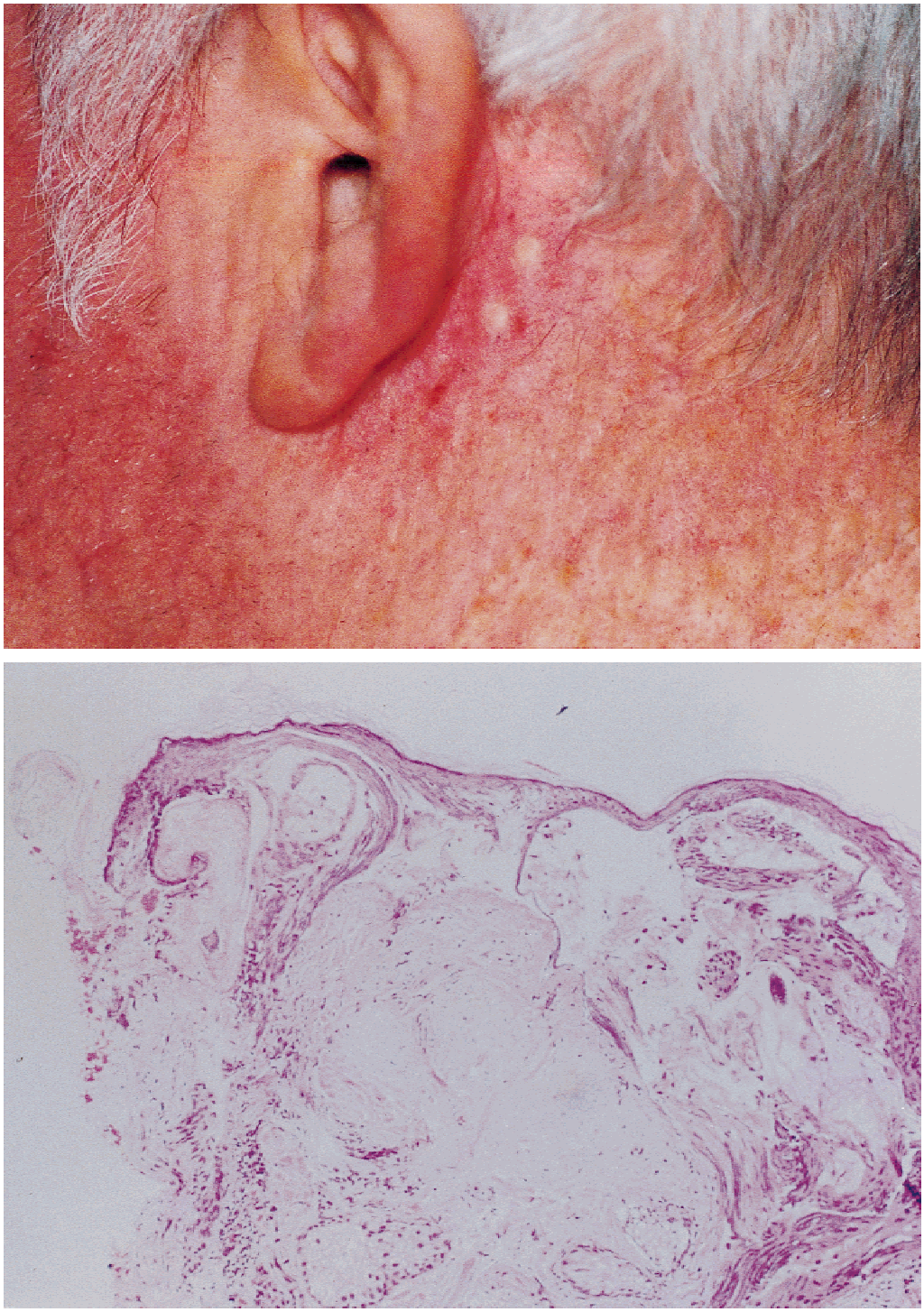

Fig. 6. Patient treated at 1,000 mJ/6 pulses (top arrow) and 1,200 mJ/4 pulses (bottom arrow) showed clinical epidermal necrosis (**top**), and histologically demonstrated full-thickness necrosis (**bottom**) deep to 1,200 μm below skin surface. Hematoxylin and eosin stain; original magnification = 40×.

subsequent remodeling of the dermis. However, selective dermal heating presumably would not improve dyspigmentation or reverse epidermal atypia.

Other investigators have proposed novel systems for nonablative skin resurfacing. Lask et al. [17] reported histologic evidence of selective dermal injury in a porcine skin model and subse-

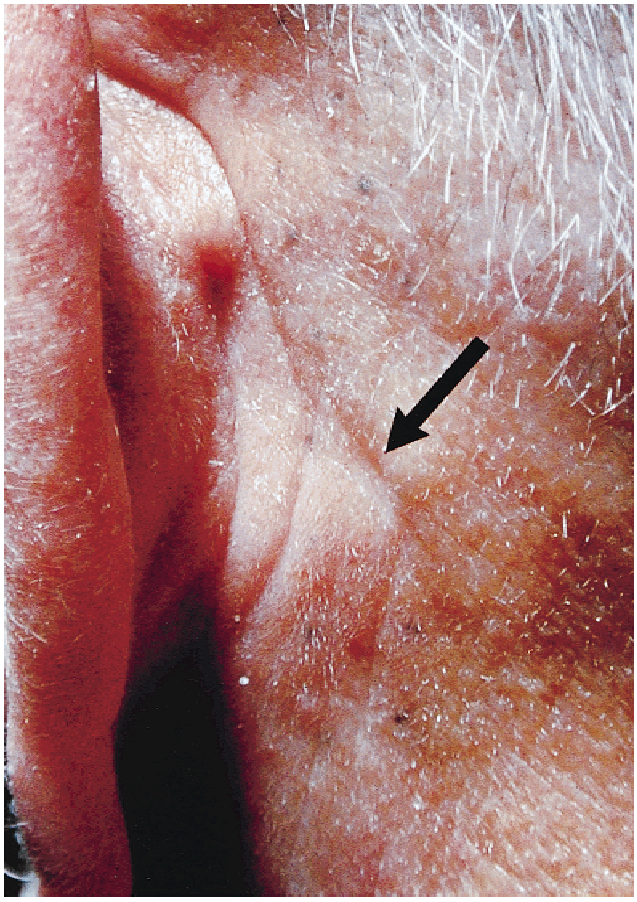

Fig. 7. Atrophic scar at the 1,000 mJ/6 pulse site 2 months later (large arrow).

quently showed clinical improvement in human facial rhytides by using a cooling cryogen spray in conjunction with a neodymium:yttrium aluminum garnet (Nd:YAG) laser operating at 1.32 μm. Muccini et al. [18] reported effective dermal remodeling by using a 980-nm diode laser with a spherical optical handpiece, which focused laser irradiation into the dermis. The focusing power of the lens allowed for concentration of energy deposition below the surface, and epidermal preservation was observed.

The level of dermal injury in nonablative techniques is partly controlled by the synchronization of surface cooling and heating. Rather than perform a rigorous analysis of the cooling and heating fronts, what follows is a discussion of first principles for any laser application designed for selective dermal heating. Heat is generated within the zone of optical penetration immediately by direct absorption of laser energy. Heating decreases with tissue depth as absorption and scattering attenuate the incident beam. The absorption coefficient for tissue water for 1.54 μm is approximately 8 cm^{-1}. Taking this value and that of the *effective* scattering coefficient (~ 6 cm^{-1}), the optical penetration depth (δ)

$$\delta \approx \frac{1}{\sqrt{3\mu_a(\mu_a + \mu_s')}} = 0.55 \text{ mm.}$$

where μ_a and μ_s' are the absorption and effective scattering coefficients, respectively [19].

Thus, the bulk of tissue heating, if not counteracted by surface cooling, will occur superficially. The instantaneous "piling up" of energy at or near the surface favors the heating front. It follows that cooling must be given a head start to succeed, i.e., the surface must be chilled before the laser exposure [20–27].With surface cooling produced by a cooled contact window, the rate of cooling depends primarily on the temperature gradient between the skin and the cooling window, and on the surface contact heat transfer coefficient. For short cooling times, the cooling will be confined to the superficial layers. When this is combined with laser heating, the peak temperature zone will be shallow in the skin. For longer cooling times, produced either by a long precooling time or continued cooling during a long laser energy delivery period, the peak temperature achieved in the skin will be deeper down.

In this study, we chose the laser heating and surface cooling parameters, with the aid of the Monte Carlo optics and thermal diffusion model, to generate peak temperature zones near a depth of 1 mm. The injuries we observed in histology are consistent with those predicted with our computer model. The accuracy of the model supports the μ_s and μ_a values as well as the cooling constants (i.e., heat transfer coefficients), used in the calculations (in the range of 2,000 to 10,000 W/m^2 – ^0K).

In retrospect, this may have been suboptimal in terms of inducing a healing response to alter the most severely photodamaged superficial dermis, because the zone of thermal injury was too deep in the dermis. A more optimal thermal injury profile for maximum improved cosmesis may be a zone of thermal injury centered more superficially.

Our erbium glass laser demonstrated a level of injury that was dependent, not unexpectedly, on pulse energy and number of pulses. For specific laser parameters, the skin demonstrated initial changes that were consistent with dermal heating (slight tinctorial changes in collagen, clumping of

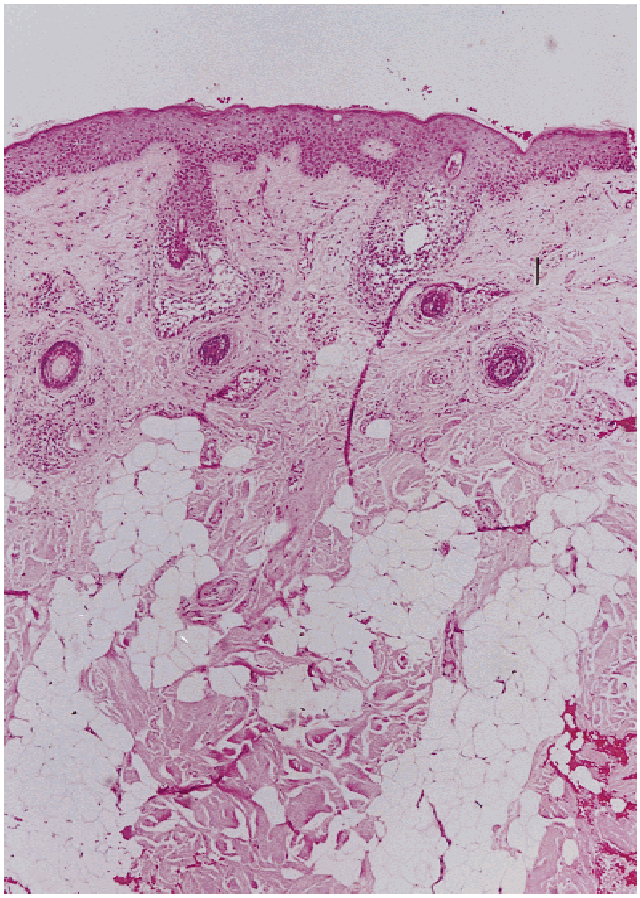

Fig. 8. Biopsy from patient immediately after treatment (800 mJ, 8 pulses, 2 passes). Hematoxylin and eosin stain; original magnification = 100×.

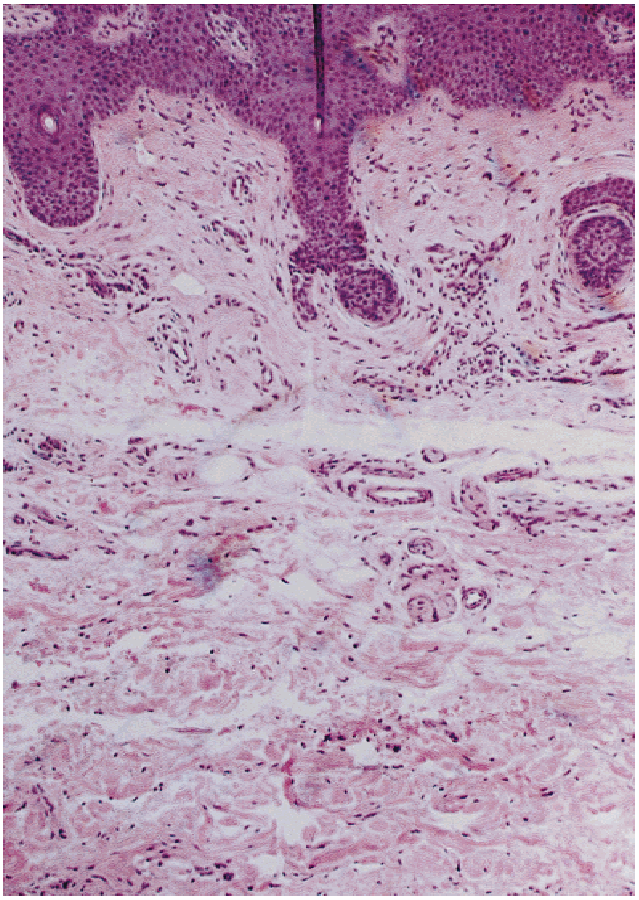

Fig. 9. Biopsy from same patient shown in Figure 8, 2 months after treatment.

basophilic collagen and elastotic material, and loss of birefringence). The greater level of dermal thermal damage on microscopy with two laser passes is not unexpected, as additional collagen presumably was recruited into the denaturation process on the second pass. Because of the interval between the first and second passes (about 3–5 seconds), the epidermis should have cooled considerably during this time (thermal relaxation time of approximately 1 msec), so that blistering was not increased by a second pass. On the other hand, the dermis would have been expected to cool less between passes, because its thermal relaxation time (at least for 1.54 μm radiation) is about 0.5 seconds.

Fibroplasia was demonstrated 2 months postoperatively in specimens where there were immediate microscopic changes. However, no reduction in incidental wrinkling was observed. The absence of wrinkle improvement might be explained, as follows. Initially, selective dermal

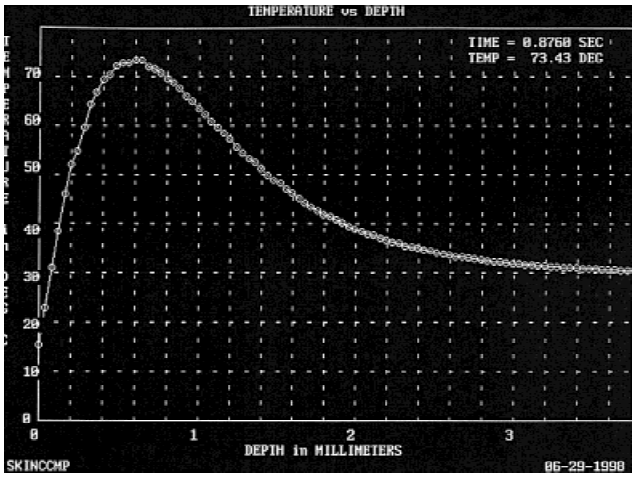

Fig. 10. Plot of temperature as a function of depth after eight pulses. Laser parameters: 1,000 mJ/pulse, 8 Hz, 2 seconds precooling, surface temperature clamped at –10°C. Note peak temperature at depth of 600 mm, μ_a = 8.3 cm^{-1}, μ_s = 60 cm^{-1}, μ_s' = 6 cm^{-1}.

heating was conceptualized with the idea that we could shrink collagen such that wrinkles would disappear akin to shrink-wrapping plastic. As we proceeded from in vitro work to in vivo work in the farm pig, it was observed that complete collagen denaturation and gross shrinkage was associated with subsequent cosmetically unacceptable scar formation. Accordingly, we decreased the thermal injury until we were able to produce transient clinical effects (edema and erythema), which did not result in significant identifiable microscopic collagen denaturation. As we followed these wounds over time, some swelling of the sites persisted, suggesting that increased glycosaminoglycans (GAG), new collagen deposition, or both, might be responsible. At these sites, however, it was difficult to identify changes from normal skin microscopically. There was no obvious increase in the number of dermal fibroblasts, and no significant increase in GAG was identified by routine mucin stains. Still, we proceeded with this human study with the idea that a well-controlled thermal insult could be delivered to the dermis without scarring but with activation of fibroblasts to produce new ECM. The end result should be increased skin turgor and therefore decreased wrinkles.

Although we observed fibroplasia in this study, it was unlike that seen after other resurfacing modalities associated with marked cosmetic improvement. Rather than being "high and tight," the fibroplasia zone was thick and deep, mirroring the initial thermal injury. The pathophysiology of superficial wrinkles is consistent with the improved cosmesis that results from a superficial zone of fibroplasia, and all presently accepted resurfacing modalities produce a 100- to 400-μM band of horizontally oriented collagen just deep to the epidermis. Additionally, after traditional resurfacing, there appears to be a diminution in the amount of solar elastosis (the microscopic hallmark of superficial wrinkles). In contrast, by sparing the epidermis with selective dermal heating, these thermally stable elastic fibers may persist, because no transepidermal elimination takes place after nonablative skin resurfacing. Thus, because of the nature of nonablative resurfacing (deep dermal heating with epidermal sparing), it is unlikely that the present heating/cooling parameters will produce this specific final histologic pattern. The deeper fibrosis induced by the greater pulse energies in our study appears to produce depressions and whitening of the skin, and is inappropriate for wrinkle reduction.

Also relevant to the failure of this laser configuration to improve wrinkles is that denatured collagen appears to be metabolized differently according to depth. Whereas superficially denatured collagen is degraded within 2 weeks, we have found that denatured collagen greater than 600 μm beneath the skin surface is associated with granulomatous inflammation; in one case, we observed denatured collagen as long as 2 months after treatment, appearing as a ball of "foreign" material. This lesion was palpated clinically as a "BB-like" nodule, and took as long as 6 months to resolve.

Finally, one should recall that dermal remodeling has been shown to occur at a depth of 100–400 μm in chemical peeling, dermabrasion, and CO_2 laser ablation [28–30]. This is intuitively attractive, as this zone is where the bulk of solar elastosis is observed in photodamaged skin. It follows that for clinically significant wrinkle reduction, heating should be spatially confined to this same zone 100–400 μm from the surface. On the other hand, by targeting the upper dermis, the "peaks" of the heating and cooling fronts are in close proximity. This proximity increases patient risk, because it demands that cooling and heating be accurate and precise. Accordingly, in the future we will explore wavelengths with higher water absorption and use more efficient cooling to confine injury to the papillary and superficial reticular dermis.

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